REMARKS

Reconsideration of the application is respectfully requested. Claim 22 has been amended to recite a daily dose range from 2.5 to 7.5 mg. Support for this amendment is found in the specification at, for example, p. 5, line 29 to p. 6, line 1. No new matter has been added. Claims 20, 22-25, 27-30, and 32-34 are pending and at issue.

Double Patenting

Claims 20, 22-25, 27-30, and 32-34 have been provisionally rejected for obviousness-type double patenting over claims 20-40 of co-pending U.S. Application No. 10/644,579 ("the '579 Application") in view of the Merck Manual (p. 440, col. 2, para. 2).

Submitted herewith is a terminal disclaimer over the '579 application. Accordingly, Applicant respectfully requests that this provisional rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

Written Description

Claims 20, 22-25, 27-30, and 32-34 have been rejected for lack of adequate written description. The Examiner contends that the claimed daily dose range of 2.5 to 10 mg is not supported by the specification. According to the Examiner, the specification discloses a "dose of 10 mg," "daily doses lower than 10 mg," and "a unit dose preparation containing 2.5 to 20 mg" (citing the specification at p. 3, lines 22-26; and p. 5, lines 29-30 and 32-34). The Examiner states that the claimed dose range of 2.5 to 10 mg is a subgenus of the disclosed unit dose range of 2.5 to 20 mg. The Examiner relies on two decisions (*In re Lukach* and *In re Smith*) as supporting the assertion that a subgenus is not supported by the disclosure of a generic range even if specific values within the generic range are also disclosed (*see* Office Action, p. 6).

The rejection is respectfully traversed, and reconsideration is requested.

Applicant submits that the cited case law does not support the Examiner's position. In *Lukach* (**Attachment A**), the applicant attempted to rely on the filing date of a grandparent application to overcome an anticipation rejection. The rejected claims were directed to copolymers having a particular molecular weight ratio range (Mw/Mn ratio). The grandparent application, however, did not disclose any particular numerical range of Mw/Mn ratios. Rather, the grandparent application only disclosed that the copolymers have a "narrow molecular weight distribution," and provided one example with one particular Mw/Mn ratio. The Court held that because the specification of the grandparent application only used the term "narrow" and did not disclose a particular numerical range, the disclosure did not support the later-claimed Mw/Mn ratio range.

Unlike the grandparent application in *Lukach*, the instant specification discloses at least two dose ranges (i.e., unit dose preparations of "2.5 to 20 mg" and daily doses of "lower than 10 mg") (*see* Specification, p. 5, lines 29-33), which, when taken together, disclose the currently claimed range (i.e., 2.5-10 mg/day). Therefore, the present situation is distinguishable from the facts in *Lukach* where no numerical range was disclosed in the grandparent application.

In *Smith* (**Attachment B**), the Court stated that a claimed subgenus is not necessarily described by a broader genus encompassing it and a species upon which it reads (*see Smith*, p. 683). The *Smith* Court further stated that determination of whether the written description requirement has been complied with should be determined on a case-by-case basis. *Id.* In the present application, and unlike the facts in *Smith*, the endpoints of the claimed dose range are explicitly disclosed (i.e., 2.5 and 10 mg).

Furthermore, with respect to numerical range limitations, "the analysis must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure." MPEP § 2163.05(III); *see also Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570 (Fed. Cir. 1985) (a temperature range of 212-380°F in the specification adequately supported a claim reciting a temperature range of 212-310°F); *In re Wertheim*, 541 F.2d 257 (CCPA 1976). In *Wertheim*, the specification stated that an extract could

be concentrated to a solids content of 25-60%, and provided examples having solids contents of 36% and 50%. The applicant amended a claim to recite the range of 35-60%. The Examiner rejected the claim for lack of written description, and the Board of Patent Appeals affirmed the Examiner's rejection. However, the Court of Customs and Patent Appeals (CCPA) reversed the Board's decision with regard to this claim and found there to be adequate written description support because "persons skilled in the art would consider processes employing a 35-60% solids content range to be part of appellants' invention and would be led by the ... disclosure so to conclude." *Id.* at 265. Here too, persons skilled in the art would consider a daily dose of 2.5 to 10 mg per day of escitalopram as part of the invention because the specification discloses a daily dose of lower than 10 mg per day, specific daily doses of 7.5 and 5 mg per day, and a unit dose preparation of 2.5 to 20 mg.

For at least the reasons set forth above, the claimed dose range of 2.5 to 10 mg of escitalopram is adequately supported by the specification. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Claims 20, 22-25, 27-30, and 32-34 have also been rejected for lack of written description support because, according to the Examiner, the specification does not adequately describe patients with "sleep disturbances," but rather merely speculates that lower dosages of escitalopram may have beneficial effects. The Examiner further argues that there "is no showing of the use of escitalopram in any patients who have suffered from sleep disturbance" (*see* Office Action, p. 7).

There is no requirement that experimental data be provided as asserted by the Examiner. Rather, the filing of a patent application serves both as conception and constructive reduction to practice of the subject matter described in the application. Thus, the inventor need not provide evidence of either conception or actual reduction to practice when relying on the content of the patent application. *Hyatt v. Boone*, 146 F.3d 1348, (Fed. Cir. 1998). MPEP § 2138.05.

The written description requirement can be satisfied by any description of "sufficient, relevant identifying characteristics" so that a person of ordinary skill in the art would recognize that the inventor had possession of the claimed invention. MPEP § 2163. Here, the specification states that "the fact that escitalopram is effective in lower doses suggests that effective treatment with less side effects may be obtained, in particular, a reduced amount of serotonin reuptake inhibitor may reduce the risk of [selective serotonin reuptake inhibitor (SSRI)]-induced ... sleep disturbances" (*see* p. 4, lines 5-8, of the specification). Therefore, the specification describes patients, who when treated with other SSRIs, have sleep disturbances (i.e., have SSRI-induced sleep disturbances). The specification also provides a contemplated dose range and specific compounds (i.e., escitalopram and salts thereof). Thus, the disclosure provides relevant, identifying characteristics so that a person of ordinary skill in the art would have recognized that the inventors had possession of the claimed invention.

Accordingly, Applicant respectfully request that this rejection be withdrawn.

Enablement

Claims 20, 22-25, 27-30, and 32-34 have been rejected as lacking enablement. According to the Examiner, the pending claims are very broad, and there are no working examples or studies of patients with sleep disturbances that are treated with escitalopram without inducing at least one sleep disturbance. The Examiner contends that because the breadth of the claims is large, and because the pharmacological art is highly unpredictable, in order to practice the invention a person of ordinary skill in the art would have to "conduct extensive research." The Examiner also asserts that "thousands" of compositions must be evaluated for their activity (*see* Office Action, p. 10).

The test for enablement is whether a person of ordinary skill in the art could make and use the invention without undue experimentation. Working examples are not required in order to satisfy the enablement requirement. MPEP § 2164.02. The Examiner's contention that the art is highly unpredictable and undue experimentation would be required because "thousands

of compositions" need to be evaluated is misplaced because the present invention specifically describes i) the drug to be administered (escitalopram or a pharmaceutically acceptable salt thereof) and, ii) specific dosage amounts (2.5 to 10 mg per day). Moreover, sleep disorders would be easy to identify given the level of expertise in the art (a fact that is supported by the very references cited by the Examiner).

Accordingly, extensive research would not be required to treat a patient suffering from depression who has a sleep disturbance when treated with an SSRI other than escitalopram. In any event, a considerable amount of experimentation is permissible, if it is merely routine. *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); MPEP § 2164.06. Here, the specification provides a narrow dose range (i.e., 2.5 to 10 mg per day), a known patient population (i.e., patient suffering from depression who has a sleep disturbance when treated with a selective serotonin reuptake inhibitor other than escitalopram), and only one therapeutic compound (escitalopram and salts thereof). These specific parameters provide those skilled in the art with adequate (in fact, detailed) guidance to perform what would be merely routine experimentation.

Finally, the Examiner has not provided a reasonable basis to establish that the claims are not enabled. The specification provides adequate guidance for the claimed method based on the disclosed parameters that are discussed above. However, the Examiner has failed to provide any reasons why this information would not permit a skilled artisan to practice the claimed invention. The Examiner appears to require an absolute showing of experimental data supporting the claimed invention. The Examiner's rejection, however, creates a much higher standard than is called for by the U.S. patent laws. Since the examiner has the initial burden to establish a reasonable basis to question enablement, the Examiner must also give reasons for the inability of a skilled artisan to practice the invention in view of the disclosed parameters (*see* MPEP § 2164.04).

For the foregoing reasons, the claims are enabled by the specification. Applicant respectfully requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 22 has been rejected as indefinite. According to the Examiner, the term "7.5 mg or less" is unclear because "or less" is not defined.

Claim 22 has been amended to recite a daily dose of "2.5 to 7.5 mg." Therefore, Applicant respectfully requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 20, 22-25, 27-30, and 32-34 have been rejected as obvious over U.S. Patent No. Re. 34,712 ("Boegesoe") in view of Bouchard (*J. Affective Dis.*, 46:51-58 (1997)) and the Merck Manual of Diagnostics, Home Ed., p. 438-47 (1997). According to the Examiner, Boegesoe teaches escitalopram and its oxalate salt, and the pharmaceutical use of escitalopram at a daily dose of 5-50 mg to treat depression. The Examiner concedes that Boegesoe does not disclose the administration of escitalopram to patients with sleep disturbances when treated with an SSRI other than escitalopram, or a daily dose of 7.5 mg. The Examiner contends that Bouchard discloses the use of citalopram with its low side effects, notably its improvement of "reduced sleep" on day 42 (*see* Office Action, p. 13). Finally, the Examiner states that the Merck Manual teaches that most depressed people have difficulty falling asleep and awaken repeatedly in the morning (*see* Merck, p. 440, col. 2). The Examiner concludes that it would have been obvious to administer a daily dose of 5-10 mg escitalopram or its oxalate salt to treat patients who have sleep disturbances when treated with an SSRI other than escitalopram without inducing sleep disturbances because the pharmacological activity of citalopram resides in escitalopram, and citalopram has advantages as an antidepressant causing fewer sleep disturbances. The Examiner also states that the claimed range of "10 mg or less" overlaps with the 5-50 mg escitalopram dose range disclosed in Boegesoe, and therefore, is *prima facie* obvious (*see* Office Action, p. 13-14).

The rejection is respectfully traversed, and reconsideration is requested.

Bouchard teaches that administration of citalopram (not escitalopram) leads to an improvement in reduced sleep (i.e., insomnia). However, this effect was noted after administering a much higher dose, i.e., 40 mg per day of citalopram, than is presently claimed (*see* Bouchard, p. 52, rt. col.). In fact, the absolute dose disclosed in Bouchard is 4-16 times higher than the claimed dose of escitalopram (or 2-8 times higher when measured on an escitalopram-only basis). Bouchard does not teach or suggest that administering a significantly lower dose (i.e., 2.5-10 mg per day of escitalopram) will not induce sleep disturbances. Boegesoe and Merck do not cure this deficiency.

Contrary to the Examiner's position, a person of ordinary skill in the art would not have been motivated to administer 2.5-10 mg per day in view of Bouchard. Rather, in view of the high dose disclosed in Bouchard that was needed to observe an effect on sleep disturbances, a skilled artisan would have been disinclined to administer the claimed low dose, and would have instead administered a higher dose commensurate with the disclosure in Bouchard. For the foregoing reasons, a person of ordinary skill in the art would also not have had a reasonable expectation of success in administering a low dose of escitalopram to achieve the desired effect.

Finally, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. The cited references fail to indicate why it would be desirable to administer a low dose of escitalopram in patients suffering from depression who have sleep disturbances when treated with an SSRI other than escitalopram. For these reasons, Applicant respectfully requests that the rejection be withdrawn.

Claims 20, 22-25, 27-30, and 32-34 have been further rejected as obvious over Feighner (*J. Clin. Psych.*, 60:12 (1999)) in view of Hyttel (*J. Neural Transm.*, 88:157-60 (1992)) and Schoffers (*Tetrahedron*, 52(11):3769-3826). According to the Examiner, Feighner teaches the use of citalopram to treat depression at a dose of 10-60 mg which on an escitalopram basis, is 5-30 mg. Feighner further discloses the use of citalopram in patients who have been treated with "other antidepressants." The Examiner contends that the Feighner study shows a decrease in

insomnia in patients treated with lower dose citalopram (see Office Action, p. 16). The Examiner concedes that Feighner does not teach the use of escitalopram or its oxalate salt.

The Examiner contends that Hyttel teaches the use of escitalopram and its crystalline oxalate salt, and shows that the pharmacological activity of racemic citalopram is attributed to escitalopram. Schoffers allegedly teaches the advantages of using chirally-pure compounds as pharmaceuticals (*see* Office Action, p. 16-17). The Examiner concludes that it would have been obvious to use a daily dose of 5-10 mg of escitalopram or its oxalate salt for treating depression without inducing sleep disturbances in patients who have sleep disturbances when treated with an SSRI other than escitalopram. According to the Examiner, a skilled artisan would have been motivated to use escitalopram because of the advantages of using a chirally-pure drug (as taught by Schoffers) and based on Hyttel's teaching that the pharmacological activity of citalopram resides in escitalopram. Because the claimed dose of escitalopram overlaps with the equivalent citalopram dose disclosed in Feighner, the Examiner contends that the claims are obvious.

The rejection is respectfully traversed, and reconsideration is requested.

Table 3 in Feighner lists insomnia as an "adverse event" in patients treated with citalopram (Feighner, p. 828). Table 3 relates to patients treated with citalopram, regardless of whether they have sleep disturbances when treated with an SSRI other than escitalopram. Therefore, the data disclosed in Feighner are not applicable to the claimed population.

Furthermore, Feighner teaches away from administering citalopram to the presently claimed population. Table 3 of Feighner shows that the incidence of insomnia in the citalopram treatment groups is higher than that of the placebo group. Thus, Feighner suggests that patients receiving citalopram actually experience more sleep disturbances than those not administered the compound. In view of these data, a person of ordinary skill in the art would not be motivated to treat the claimed population with citalopram or escitalopram because Feighner demonstrates that citalopram increases the incidence of sleep disturbances. Therefore, Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

In view of the above remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: August 2, 2007

Respectfully submitted,

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